REMARKS

The Official Action dated February 24, 2004 has been carefully considered. Accordingly, the change presented herewith and the following remarks are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

Claim 65 has been amended to correct a typographical error. It is believed this change does not involve any introduction of new matter and does not raise any new issues after final rejection. Entry of this amendment is therefore believed to be in order and is respectfully requested.

Claims 42, 43, 47, 51-53, 56, 57, 59-61, 63, 64, 68, 72-74, 77, 78 and 80-82 were rejected under 35 U.S.C. §103(a) as being unpatentable over the Charlton et al U.S. Patent No. 5,989,921 in view of the Batz et al U.S. Patent No. 4,415,700 and the Brown et al U.S. Patent No. 5,149,622. The Examiner asserted that Charlton et al disclose an immunoassay method and device with a test site comprising latex particles entrapped or fixed in the flow path and having an immobilized protein (antibody/capturer) on their surface. The Examiner admitted that Charlton et al fail to teach immobilized particles which exhibit hydrophilic groups on their surfaces or that the particles have a size which is smaller than the smallest inner dimension of the flow channels of the matrix. The Examiner asserted that Batz et al disclose hydrophilic particles as a carrier for biologically and/or immunologically active substances covalently bound to the particles for use in immunoassays. The Examiner asserted that Brown et al disclose a fluid device in which particles having a substance capable of reaction with an analyte in a sample are immobilized in a matrix, wherein a particle of a size smaller than the flow channels of the matrix is used to provide an improved solid-phase analytical device.

Claims 44-46 and 65-67 were rejected under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of the newly cited Bennich et al U.S. Patent No. 3,720,760. The Examiner relied on Bennich et al as disclosing test allergens immobilized to particles and disclosing that the test allergen can be a mixture of two or more allergens. The Examiner asserted it would have been obvious to incorporate test allergens taught by Bennich et al into the modified method of Charlton et al.

Claims 48, 50, 54, 55, 69, 71, 75 and 76 were rejected under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of the Devlin et al U.S. Patent No. 5,846,703. The Examiner asserted it would have been obvious to incorporate the use of immobilized antigens as taught by Devlin et al into the modified method of Charlton et al. Claims 49, 58, 70 and 79 were rejected under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of the Dafforn et al U.S. Patent No. 4,981,786. The Examiner asserted it would have been obvious to incorporate the application of reagents and the detection of autoimmune antibodies as taught by Dafforn et al into the modified method of Charlton et al. Finally, claims 62 and 83 were rejected under 35 U.S.C. §103(a) as being unpatentable over Charlton et al, Batz et al and Brown et al in view of the Self U.S. Patent No. 4,446,231. The Examiner asserted it would have been obvious to use immunoassays as taught by Self for the diagnosis of autoimmune diseases.

However, Applicants submit that the methods and test kits defined by claims 42-83 are nonobvious over and patentably distinguishable from the combination of Charlton et al, Batz et al and Brown et al, even in further view of Bennich et al, Devlin et al, Dafforn et al or Self. Accordingly, these rejections are traversed and reconsideration is respectfully requested.

More particularly, as defined by claim 42, the present invention is directed to a method for detecting an analyte in a sample in a flow matrix by use of biospecific affinity reaction. The method comprises allowing an analytically detectable reactant (Reactant*) and the sample comprising the analyte to migrate through channels in a flow matrix to a detection zone located in the matrix, in which there is a firmly anchored biospecific affinity reactant (Capturer), and capturing the Reactant* in the detection zone in an amount related to the amount of analyte in the sample. According to claim 63, the invention is directed to a test kit for performing analytical methods in a flow matrix utilizing biospecific affinity reactions to detect an analyte in a sample. The kit comprises (i) a flow matrix having a detection zone in which there is firmly anchored biospecific affinity reactant (Capturer), and (ii) an analytically detectable reactant (Reactant*).

In both the claimed methods and test kits, the Reactant* has labeled particles as an analytically detectable group, and the Capturer is anchored to the matrix by immobilized particles which exhibit hydrophilic groups on their surface. The particles anchoring the Capturer have a diameter smaller than a smallest inner dimension of the flow channels of the flow matrix and do not interfere with detection of Reactant* in the detection zone. Thus, the Capturer is predisposed in the flow channels of the flow matrix by the immobilized particles exhibiting hydrophilic groups on their surface. As set forth in the present specification, including the examples, such methods and test kits wherein the Reactant* has labeled particles as an analytically detectable group and the Capturer is anchored within the flow channels of the matrix by immobilized particles which exhibit hydrophilic groups on their surface, provide surprisingly improved analytical detection of an analyte in a sample.

In this regard, attention is directed to the specification, for example at page 4, line 15 - page 5, line 12 wherein the marked hydrophobic character of polystyrene particles is

discussed. While the hydrophobicity of polystyrene causes it to be adsorbed very strongly to nitrocellulose flow membranes, the hydrophobic features of the particles have been found to promote non-specific adsorption of labeled reactant (Reactant*) and/or analyte, thereby decreasing the sensitivity of test methodologies. On the other hand, the methods and test kit according to the invention, wherein the Capturer is anchored to the matrix by immobilized particles which exhibit hydrophilic groups on their surface, promote covalent bonding of biospecific affinity reactants to the particles and as such decreases the tendency of non-specific adsorption of labeled reactant and/or analyte in a detection zone.

Charlton et al disclose a test cell and a method for detection of a preselected ligand in a liquid sample. Charlton et al disclose that the method involves the step of transporting the sample and a conjugate comprising a protein bound to a metal sol or other colored particle along a flow path and in contact with a test site comprising immobilized binding protein specific to an epitope of the ligand. Charlton et al broadly disclose that the test site comprises latex particles trapped or otherwise fixed in the flow path having the immobilized protein on their surface (column 3, lines 25-37), and specifically disclose the use of latex beads comprising polystyrene particles passively coated with purified rapid anti-human chorionic gonadotropin (column 7, lines 61-64).

However, Applicants find no teaching or suggestion by Charlton et al relating to a method or test kit as defined in claims 42 and 63 wherein a biospecific affinity reactant (Capturer) is firmly anchored to a flow matrix via immobilized particles exhibiting hydrophilic groups on their surface, particularly in combination with an analytically detectable reactant (Reactant*) having labeled particles as an analytically detectable group. As discussed above, the present specification notes, for example, beginning at page 4, line 21, that while a hydrophobic particle such as the polystyrene employed by Charlton et al is

absorbed very strongly to flow matrices such as nitrocellulose membranes, the hydrophobic features of the particles promote non-specific absorption of analytically detectable reactant (Reactant*) and/or analyte and therefore decrease the specificity and accuracy of assays. In the present invention, the immobilized particles which anchor the Capturer to the matrix exhibit hydrophilic groups on their surface. As the specification notes, for example beginning at page 5, line 8, introduction of the hydrophilic groups on the particles facilitates covalent binding of biospecific affinity reactants to the particles and decreases the tendency of non-specific absorption in the detection zone. Applicants find no teaching or suggestion by Charlton et al relating to immobilized particles exhibiting hydrophilic groups on their surface, or any advantage provided thereby.

The deficiencies of Charlton et al are not resolved by Batz et al and Brown et al. For example, Batz et al disclose hydrophilic latex particles consisting of a homo- or a co-polymer of monomers which are sparingly soluble in water and a process for the preparation of such particles. Batz et al further disclose the use of such particles as carrier materials for biological and/or immunologically active substances in diagnostic agents. Particularly, as demonstrated in Examples 10-13 at columns 8-12 of Batz et al, the particles are used for solution immunoassays (see, for example, column 9, lines 50-60; column 10, line 58 - column 11, line 6; and column 11, lines 17-49). Applicants find no teaching or suggestion by Batz et al relating to a flow matrix immunoassay or use of the latex particles described therein in a flow matrix immunoassay. In fact, Applicants find no teaching or suggestion by Batz et al that their latex particles are suitable for adsorbtion to a second solid support or matrix. Moreover, Applicants find no teaching, suggestion or recognition by Batz et al that their particles will provide improved sensitivity in flow matrices and decrease the tendency of non-specific absorption in a detection zone as is obtained according to the present invention.

In the Official Action, the Examiner asserted that it is within the realm of ordinary skill in the art to replace one solid phase particle (that of Batz et al) for another solid phase particle (that of Charlton et al) because the use of such particles is well known in the art. However, obviousness cannot be established by combining the teachings of the prior art to produce a claimed invention absent some teaching, suggestion or incentive supporting the combination, *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *In re O'Farrell*, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988). Clearly, that two references relate to the same general technology is not sufficient as the prior art which the Federal Circuit found deficient in *Geiger* all related to water treatment technology. Nevertheless, the Court found that the requisite teaching, suggestion or incentive supporting the combination of prior art was absent. Similarly, in the present rejection, that Charlton et al and Batz et al each disclose particles for use in assay techniques is not sufficient absent some teaching, suggestion or incentive supporting the combination. To the contrary, in view of the disclosures of Charlton et al and Batz et al, at best, one skilled in the art might find it obvious to try various combinations of their disclosures. However, as noted by the Court in *Geiger*, this is not the standard for patentability.

The Examiner appears to rely on the disclosure of Batz et al indicating that their hydrophilic particles provide a diagnostic agent which has covalently bound biological and/or immunological active substances which do not impair the structure and thus the activity of the biologically active proteins. However, in view of Batz et al's concern for impairment of reactant activity, one of ordinary skill in the art would be disinclined to absorb such particles to a second solid support, as one of ordinary skill in the art would presume that such adsorption would impair the structure and thus the activity of the biologically active proteins with which Batz et al are concerned. Thus, the concerns which Batz et al attempt to

overcome would lead one of ordinary skill in the art away from the combination asserted by the Examiner. It is error to find obviousness where references diverge from and teach away from the invention at hand, *In re Fine*, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988). Thus, Batz et al do not resolve the deficiencies of Charlton et al.

Brown et al disclose a solid-phase analytical device for use in solid-phase binding assays to determine the presence or amount of an analyte in a test sample. In the paragraph bridging columns 8 and 9, Brown et al disclose the use of substantially spherical solid particles retained and immobilized upon fibers of a porous fiber matrix material. Brown et al specifically disclose that

> "the size of the particles is not critical, and so long as the average diameter of the particles is substantially within the aforestated range (although it is preferred that the average diameter of the particles be smaller than the average pore size of the fibrous matrix), any type of particles having the foregoing properties is suitable for use" (column 9, lines 11-17).

The referenced range is from about 0.1 to about 10 microns or more, most preferably from about 0.1 to about 5 microns (column 8, lines 53-56). However, Applicants find no teaching by Brown et al that the particle size is smaller than the flow channels of the matrix or, as required by the present claims, that the *particles have a diameter smaller than a smallest inner dimension of the flow channels of the flow matrix.* To the contrary, Brown et al merely refer to *average* diameters. Thus, Brown et al neither teach nor suggest the limitations required by the present claims.

As Brown et al fail to teach or suggest the limitation of the present claims that the particles have a diameter smaller than a smallest inner dimension of the flow channels of the flow matrix, the combination asserted by the Examiner of Charlton et al and Brown et al does not result in a flow matrix to which capturer is anchored as required by the present claims. At page 12 of the Official Action, the Examiner again notes that Brown et al teach the

average diameter of the particles is less than the average pore size of the matrix, again failing to appreciate the difference between this teaching in Brown and the limitations required by claims 42 and 63. The Examiner further asserts that the optimum dimension in diameter of the flow channels and particle size can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art. However, it is not obvious to optimize a parameter not recognized as a result-effective variable, *In re Antonie*, 195 U.S.P.Q 6 (CCPA 1977), and Brown et al provide no teaching or suggestion as to any import of particle size. To the contrary, Brown et al disclose that the size of the particles is not critical (column 9, lines 11-17).

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). As noted, Batz et al fail to teach or suggest the use of their latex particles in a flow matrix or in combination with any other type of solid support, and Brown et al fail to teach a method and flow matrix as presently claimed, wherein particles anchoring the Capturer have a diameter smaller than a smallest inner dimension of the flow channels of the flow matrix and do not interfere with detection of Reactant* in the detection zone. In view of these deficiencies, Batz et al and Brown et al in combination with Charlton et al do not enable one of ordinary skill in the art to make and use the presently claimed methods and test kits. It is therefore submitted that the methods and test kits defined by claims 42, 43, 47, 51-53, 56, 57, 59-61, 63, 64, 68, 72-74, 77, 78 and 80-82 are nonobvious over and patentably distinguishably from the combination of Charlton et al, Batz et al and Brown et al, whereby the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

Moreover, the deficiencies of Charlton et al in view of Batz et al and Brown et al are not resolved by the newly cited Bennich et al reference. That is, Bennich et al disclose an in vitro method for determining the presence of reagin-Ig in a sample wherein a test allergen comprising one single allergen or a mixture of two or more allergens may be employed (column 4, lines 56-57). However, Bennich et al, like Batz et al, relate to a method wherein particles are contacted with a sample in a solution, and Applicants find no teaching or suggestion by Bennich et al relating to the use of a flow matrix as required by the present claims. Accordingly, the teachings of Bennich et al do not resolve the basic deficiencies of the combination of Charlton et al, Batz et al and Brown et al. That Bennich et al teach the use of a combination of allergens in a process in which particles are contacted with a sample in a solution is not relevant to the patentability of the presently claimed methods and test kits which employ a flow matrix and are directed to the objective of improving the specificity and accuracy of methods and test kits employing a flow matrix. It is therefore submitted that the rejection under 35 U.S.C. §103 based on Charlton et al, Batz et al, Brown et al and Bennich et al has been overcome. Reconsideration is respectfully requested.

Similarly, the deficiencies of Charlton et al in view of Batz et al and Brown et al are not resolved by any of the remaining references cited by the Examiner. For example, Devlin et al disclose fluorescence immunoassays using fluorescent dyes free of aggregation and serum binding. Devlin et al broadly disclose that the sandwich techniques disclosed therein can be used to assay antibodies rather than antigens wherein the antigen coupled to a solid phase is used as a first receptor. Beginning at column 4, line 56, Devlin et al briefly discuss the use of enzyme-enhanced fluorescence technology which combines microparticle capture and antigen-antibody reaction with an enzyme rate reaction using a fluorescent enzyme substrate.

However, Applicants find no teaching or suggestion by Devlin et al relating to a method or test kit as presently claimed, or for modifying the teachings of Charlton et al to provide such a method or test kit. Particularly, Applicants find no teaching or suggestion by Devlin et al for a method or test kit employing a flow matrix as presently claimed wherein an analytically detectable reactant (Reactant*) has labeled particles as an analytically detectable group and a biospecific affinity reactant (Capturer) is anchored to the flow matrix via immobilized particles of a size and function as claimed and exhibiting hydrophilic groups on their surface. Similarly, Applicants find no teaching or suggestion by Devlin for modifying the teachings of Charlton et al to provide such a combination, or relating to any benefit provided by either a flow matrix method or test kit employing such a combination.

The cited combination of Charlton et al, Batz et al, Brown et al and Devlin et al does not enable one skilled in the art to conduct the claimed methods or to make and use the claimed test kits. Thus, these references do not in combination render the presently claimed methods and test kits obvious, *Motorola, Inc. v. Interdigital Tech. Corp., supra.* It is therefore submitted that the rejection under 35 U.S.C. §103 based on Charlton et al, Batz et al, Brown et al and Devlin et al has been overcome. Reconsideration is respectfully requested.

Dafforn et al disclose a multiple port assay device for capturing a first member of a specific binding pair in a zone and for allowing liquid to be transported by capillary action away from the zone. Delivery of a sample may be made into the device through a first means using a dropper, syringe needle, etc., resulting in deposit of the sample on a bibulous strip, and a liquid reagent other than sample may be added to the device through a second means. Additional liquid reagents may be added to the device either before or after sample addition,

at least one of such reagents being added through the means not used for adding the sample (column 13, lines 32-42).

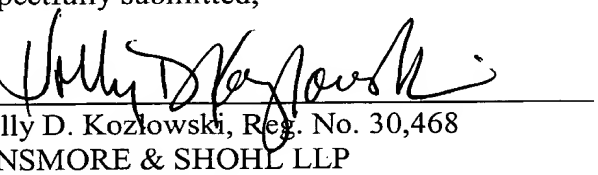
However, Applicants find no teaching or suggestion by Dafforn et al relating to a method or test kit as presently claimed employing, in combination, an analytically detectable reactant (Reactant*) having labeled particles as an analytically detectable group and a Capturer which is anchored to the matrix by immobilized particles as defined and exhibiting hydrophilic groups on their surface. Similarly, Applicants find no teaching or suggestion by Dafforn et al relating to any improvement provided by a method or a test kit employing such a Reactant* and immobilized Capturer in combination. Finally, Applicants find no teaching or suggestion for modifying the teachings of Charlton et al to incorporate any or all of the teachings of Dafforn et al, and particularly Applicants find no teaching or suggestion in either reference for modifying the teachings of Charlton et al along the lines of the presently claimed methods and test kits. In view of these deficiencies in the teachings of Dafforn et al, the combination of Dafforn et al with Charlton et al, Batz et al and Brown et al does not enable one of ordinary skill in the art to perform the presently claimed methods or to make and use the claimed test kits. Thus, the combination of Charlton et al, Batz et al, Brown et al and Dafforn et al does not render the presently claimed methods and test kits obvious under 35 U.S.C. §103. It is therefore submitted that the rejection under 35 U.S.C. §103 based on Charlton et al, Batz et al, Brown et al and Dafforn et al has been overcome. Reconsideration is respectfully requested.

Finally, Self discloses an immunoassay using an amplified cyclic detection system. At column 1, beginning at line 39, Self broadly discloses that immunoassays may be used for qualitative or quantitative determinations and that color reactions and precipitation reactions, for example, using latex particles for visualization, may be used. However, Applicants find

no teaching or suggestion by Self relating to methods or test kits as presently claimed employing a combination of an analytically detectable reactant (Reactant*) having labeled particles as an analytically detectable group and a biospecific affinity reactant (Capturer) anchored to a flow matrix via immobilized particles as claimed which exhibit hydrophilic groups on their surface. Similarly, Applicants find no teaching or suggestion by self for modifying the teachings of Charlton to provide such methods or test kits, or relating to any advantage provided thereby. Thus, the combination of Charlton et al, Batz et al, Brown et al and Self does not enable one of ordinary skill in the art to conduct the presently claimed methods or to make and use the presently claimed test kits. Accordingly, the combination of Charlton et al, Batz et al, Brown et al and Self does not render the presently claimed methods and test kits obvious. It is therefore submitted that the rejection under 35 U.S.C. §103 based on Charlton et al, Batz et al, Brown et al and Self has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the rejections under 35 U.S.C. §103, and places the present application in condition for allowance. Reconsideration and an early allowance are requested. In the event that the present Amendment does not place this application in condition for allowance, entry of the present Amendment for purposes of appeal is requested.

Respectfully submitted,

By 

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